

(12)

EUROPEAN PATENT APPLICATION

(21) Application number: 85830154.2

(51) Int. Cl.⁴: **A 61 K 31/455**
A 61 K 9/52

(22) Date of filing: 19.06.85

(30) Priority: 29.06.84 IT 351184

(43) Date of publication of application:
15.01.86 Bulletin 86/3

(84) Designated Contracting States:
AT BE CH DE FR GB LI NL

(71) Applicant: **Valducci, Roberto**
Via del Sole, 4
I-47039 Savignano sul Rubicone (Forlì)(IT)

(72) Inventor: **Valducci, Roberto**
Via del Sole, 4
I-47039 Savignano sul Rubicone (Forlì)(IT)

(74) Representative: **Lanzoni, Luciano**
c/o BUGNION S.p.A. Via Farini, 37
I-40124 Bologna(IT)

(54) **Process for preparing etofibrate or similar compounds containing sustained release microgranules and products thus obtained.**

(57) The present invention relates to the pharmaceutical field and particularly to the manufacturing of a pharmaceutical product named etofibrate in the form of sustained release microgranules, wherein each microgranule consists entirely of an etofibrate composition and polyethylene glycol 4000, said microgranules being placed in capsules that, size of known capsules being equal, display an higher concentration of the active ingredient, the process for preparing the above microgranules comprising mainly the manufacturing of a compound consisting of etofibrate and solvent, wherein said compound is obtained in rotatory pan, then submitting this compound to a first sieving, placing it again in rotatory pan, drying the product thus obtained and sieving it once more, separating the microgranules which are replaced in the rotatory pan and then coated in rotatory pan with further etofibrate added with a suitable amount of polyethylene glycol 4000 to give, after a last sieving, the desired microgranules whose size corresponds to the requested size and is normally comprised between 400 and 2000 microns.

- 1 -

Process for preparing etofibrate or similar compounds
containing sustained release microgranules and products
thus obtained

- 5 The present invention relates to a new composition of etofibrate microgranules which are differently formulated and differently manufactured in comparison to the already available product.
- 10 Etofibrate is in fact a known compound having the following pharmacological properties: it reduces hyperlipidemia, hypertriglyceridemia and hypercholesterolemia. Said etofibrate is a compound corresponding to the chemical name 2-(p-chlorophenoxy) - 2 - methylpropionic acid
15 [2-(nicotinoyloxy)-ethyl] - ester . This product is on the market since many years and is available in form of hard "00" type gelatine capsules containing 500 mg of etofibrate as sustained release microgranules. These capsules, with a capacity of 0.95 ml, are able to contain
20 the above microgranules which are composed of an inert material inner core coated with a spheroidal layer of active ingredient comprising etofibrate and polyethylene glycol 4000, also known on the market as polyglycol 4000. This result, that has been achieved by means of
25 particular per se known processes, entails each microgranule to have a concentration ranging from 67 to 75% of active ingredient, as even each microgranule consists also of an inert material inner core with a diameter of 850-500 microns comprising from 65 to 90% of sucrose
30 and from 10 to 35% of corn starch. The presence in each microgranule of an inner core binds evidently to use the above "00" type capsules, being only these capsules

- 2 -

able to contain the mentioned dosage of 500 mg per capsule.

Aim of the present invention was to obtain an higher concentration of etofibrate, so that the 500 mg standard dosage might be placed in smaller gelatine capsules. In each capsule an higher dosage of 750 mg of active ingredient may also be included.

10 It is therefore possible to have the 500 mg standard dosage placed not in the "00" type capsules but rather in a "0" type capsule (0.68 ml), thus evidently facilitating its deglutition.

15 Because of components percentage and of its particular constitution, this composition allows a sustained release of the drug and eliminates the well-known flash, characteristic side-effect of etofibrate. Further aim of the present invention was to prepare spherical
20 microgranules by means of simple procedures, said microgranules having a diameter ranging from 400 to 2000 microns and an etofibrate concentration of 88-98%, in other words spherical microgranules without inert core and, therefore, with an higher concentration of active
25 ingredient.

This and other aims have been achieved with the present invention, characterized in that the provided process comprises the following manufacturing features:

30 - preparation in rotatory pan of a compound consisting of etofibrate and solvent, said compound being then submitted to a first sieving and replaced in rotatory

- 3 -

pan, the product being subsequently dried and resieved,
the microgranules being separated and then introduced
in rotatory pan, wherein the microgranules thus obtained
are coated with further etofibrate added with a suitable
5 percentage of polyethylene glycol 4000 to give, after
a last sieving, the ultimate microgranules having a
size corresponding to the requested size and which is
normally comprised between 400 and 2000 microns.

10 The product obtained with the above process consists
at contrary of a "O" type (0.68 ml), or "O" extended
type (0.80 ml) or of a "OO" type capsule (0.95 ml)
containing respectively 500, 600 or 750 mg of active
ingredient, wherein said active ingredient consists of
15 several microgranules having a diameter between 400
and 2000 microns, each microgranule comprising an eto-
fibrate inner core and an outer coat of etofibrate added
with polyethylene glycol 4000, wherein the total
percentage of etofibrate is comprised between 89 and
20 98%, whereas the total percentage of polyethylene
glycol 4000 ranges from 11 and 2% respectively.

From what stated above, it may be clearly argued that,
in comparison to the prior art, each capsule is filled
25 with many microgranules, all being lacking in inert
core and, therefore, at high concentration of active
ingredient, and having particular percentages of the
active ingredient compositions which confer the mention-
ed advantages. Further features and advantages of the
30 invention will be made clear in the following detailed
description that is given only for illustrative but
not limitative purposes.

- 4 -

The process used to obtain the product of the present invention provides the following procedures, each being only given as exemplificatory.

- 5 Generally, the process comprises the following steps:
- a) powdered etofibrate (or a substance having similar properties) was placed in a rotating pan, then solvent was added and the mixture was worked in the same pan;
 - 10 b) the compound was submitted to a first sieving and the first microgranules thus obtained were reworked in the pan that was being rotated for a while;
 - c) the product comprising these first microgranules was dried until the solvent was evaporated off, then
15 it was sieved again thus separating other microgranules or cores having a pre-determined diameter, which however is lower than the diameter of the first microgranules;
 - d) said second microgranules or cores were replaced in
20 the rotating pan and, by means of suitable pumps or by spraying, they were coated with further etofibrate to which a suitable amount of polyethylene glycol 4000 has been added;
 - e) a last sieving was carried out to separate only
25 these third microgranules, whose size corresponds to the requested size and is comprised between 400 and 2000 microns;
 - f) said third microgranules were then placed in suitable capsules.

30

A detailed example of the process described above is reported here below.

Referring to an amount of 50 kg of etofibrate, this powder was placed in a pan having a steel basket rotating at 10-20 rpm; 10 kg of acetone were added and the pan was being rotated for 10-25 minutes.

5

The product was discharged and placed in a net granulator of 14-20 mesh. The granulate thus obtained (or first microgranules) was replaced in the pan, rotating for 10/25 minutes. The product was dried for 10 10/20 minutes at 30°C in a thermostatic drier, i.e. until all the acetone was evaporated off.

The dried granulate was then resieved, thus selecting the fraction comprised between 300 and 1000 microns 15 and consisting of the second microgranules or cores. Said fraction was placed in the rotating pan and by spraying with high pressure pumps the cores were coated with previously fused etofibrate to which polyethylene glycol 4000 was added. As to the sprayed etofibrate, 20 the amount of polyethylene glycol 4000 is comprised between 3 and 12%. These (third) microgranules thus obtained were sieved for a last time and they were showing a diameter comprised between 400 and 2000 microns.

25

A further procedure could be fully identical to the procedure described above, with the sole exception that the etofibrate applied on the previously formed cores was not melted in advance.

30

For coating these nuclei with etofibrate, the product was brought into solution with a solvent (acetone) by

- 6 -

preparing a cold saturated solution or, if a lower concentration is desired, the solution etofibrate-acetone was heated between 35° and 45°C. In both cases, to the etofibrate solution the 3-12% of polyethylene glycol 4000, based on the etofibrate, was added. The microgranules obtained with the procedures and methods described above were then placed into capsules that are well known in the art as hard gelatine capsules and that can be of several sizes, that is of "O" type, containing 0.68 ml, or of extended "O" type (0.80 ml) or of "00" type (0.95 ml).

The product obtained with the above process consists therefore of one of said capsules containing respectively 500, 600 or 750 mg of active ingredient. Said active ingredient comprises all the (third) microgranules having a diameter ranging from 400 to 2000 microns. Each of these microgranules consists therefore of an etofibrate inner core and of an outer layer of etofibrate added with polyethylene glycol 4000, according to the above process, the whole having amounts of etofibrate ranging from 89 and 98% and amounts of polyethylene glycol 4000 comprised between 11 and 2% respectively. Evidently each microgranule consists mainly and entirely of active ingredient, even though it comprises an inner core of etofibrate alone. Logically each microgranule consists entirely of active ingredient with a very high amount of etofibrate, and therefore all the microgranules corresponding to a standard dosage of pharmaceutical product will take up less room and less volume, so that on one hand the therapeutic activity of the capsules can be increased, size of known capsules being equal,

0168360

- 7 -

and on the other hand their size may be decreased,
amount of active ingredient being equal.

C l a i m s

1. A process for preparing etofibrate or similar compounds containing sustained release microgranules, characterized in that it comprises the following manufacturing steps :
- a) powdered etofibrate or similar substance is placed in a rotating pan, a solvent is added, and the mixture is worked in said pan;
 - 10 b) the compound is submitted to a first sieving and the microgranules thus obtained are reworked in the pan which is being rotated;
 - c) the product comprising these first microgranules is dried until the solvent is evaporated off, and then
15 it is dried again thus obtaining other microgranules or cores having the desired diameter which is lower than the diameter of the first microgranules;
 - d) said second microgranules or cores, obtained as described under c), are replaced in the rotating
20 pan and by means of suitable pumps they are coated with further etofibrate or similar substance to which a suitable amount of polyethylene glycol 4000 has been added;
 - e) a last sieving is carried out in order to separate
25 only the third microgranules whose size corresponds to the requested size, it being however higher than the size of the second microgranules;
 - f) said third microgranules are placed in capsules.
- 30 2. A process according to claim 1, characterized in that:
- in step (a) the solvent amount by weight corresponds to 10-40% of the etofibrate weight, said pan being

rotated at a speed comprised between 10 and 20 rounds per minute and for a time ranging between 10 and 25 minutes;

- in step (b) said compound is transferred to a granulator having from 14 to 20 mesh and the first microgranules thus obtained are being rotated in the pan for a time of 10-25 minutes;
- in step (c) the product consisting of the first microgranules is dried for 10/20 hours at about 30°C, said second microgranules having a diameter comprised between 300 and 1000 microns;
- in step (d) these second microgranules are coated with previously melted etofibrate by means of high pressure pumps, wherein the etofibrate is added with polyethylene glycol 4000, its amount being the 3-12%, based on the sprayed etofibrate;
- in step (e) these third microgranules are sieved to give a product having a diameter comprised between 400 and 2000 microns.

20

3. A process according to claim 1, characterized in that in step (d) the etofibrate, to which polyethylene glycol 4000 is to be added and that is to be applied on the second microgranules, is brought into solution with a solvent, creating a cold saturated solution, and then polyethylene glycol 4000 is added.

4. A process according to claim 1, characterized in that in step (d) the etofibrate to be added with polyethylene glycol 4000 and to be applied on the second microgranules or cores is brought in solution with a solvent, then suitably heated and added with

- 10 -

polyethylene glycol 4000.

5. A process according to claims 1, 3 or 4, characterized in that the solvent is acetone.

5

6. A product obtained with the above process, characterized in that it comprises a "O" type (0.68 ml) or an extended "O" type (0.80 ml) or a "OO" type (0.95 ml) capsule, containing respectively 500 mg, 600 mg or 750
10 mg of active ingredient, this comprising several microgranules having a diameter of 400-2000 microns, each of said microgranules consisting of an etofibrate inner core and of an etofibrate outer layer to which polyethylene glycol 4000 is added, wherein the whole
15 comprises amounts of etofibrate of 89-98% and amounts of polyethylene glycol 4000 of 11-2%.

7. A process for preparing etofibrate or similar compounds containing sustained release microgranules
20 and a product obtained with this process as described in the previous claims.

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.